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(71) Applicant *(for all designated States except US)*: **MICIO PHARMA CHEMICAL AKTIENGESELLSCHAFT** [LI/LI]; c/o Firmata Treuhand Anstalt, Landstrasse 35, Postfach 1138, FL-9490 Vaduz (LI).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **DE TOMMASO, Vincenzo** [IT/IT]; Residenza Alberata, 352, I-20080 Basiglio (IT).

(74) Agents: **BARCHIELLI, Giovanna** et al.; Ufficio Internazionale Brevetti Ing. C. Gregorj S., Ing. C. Gregorj S.p.A., Via Dogana, 1, I-20123 Milan (IT).

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(54) Title: RETARD FORMULATION OF AMOXICILLIN FOR ORAL ADMINISTRATION

(57) Abstract: The present invention refers to a pharmaceutical formulation of amoxicillin for oral administration, comprising a homogeneous mixture of amoxicillin and one or more polysaccharides, wherein the polysaccharide is selected from the group consisting of regenerated cellulose, cellulose ethers or esters, xanthan gum or carrageenan.

RETARD FORMULATION OF AMOXICILLIN FOR ORAL ADMINISTRATION

The present invention refers to a retard pharmaceutical formulation of amoxicillin.

Amoxicillin is a semi-synthetic, widely used, penicillin especially for oral administration, having a broad-spectrum of activity.

The orally administered amoxicillin is rapidly adsorbed, reaching, 2 hours after the administration of 250 mg, a peak concentration in the plasma of about 5 µm/ml.

The daily dose of amoxicillin is generally of 3 g for adults and of 100 mg for children per kg of body weight, divided into three administrations. Amoxicillin, as the other penicillins, has a relatively short half-life (0.9-2.5 hours) and it is therefore necessary to undertake three administrations per day, regularly spaced out, in order to maintain the therapeutic levels of the antibiotic in the blood.

Obviously, the fact that the antibiotic has to be taken every 8 hours, especially in the case of children, is very inconvenient. Furthermore, the concentration of the antibiotic in the blood widely varies in correlation to the three administrations.

The present invention refers to a retard pharmaceutical formulation of amoxicillin for oral administration, comprising a homogeneous mixture of amoxicillin and one or more polysaccharides.

Amoxicillin may be in any state of hydration.

The polysaccharide is chosen from the group consisting of regenerated cellulose, cellulose ethers or esters, xanthan gum or carrageenan.

The cellulose ethers or esters are preferably methylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose.

The ratio between amoxicillin trihydrate and the polysaccharide may vary from 100:1 to 100:40, preferably from 100:7 to 100:9.

Furthermore the formulation may contain a clavulanic acid salt, preferably the potassium salt.

The formulation may contain a surfactant, for example a phospholipid, natural or synthetic (hydrogenated phospholipid). Exampl s of phospholipids are

phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine and their hydrogenated forms. Particularly preferred is the hydrogenated phosphatidylcholine.

Other excipients, such as stabilizing agents, preservatives, antioxidants, flavouring agents, sweeteners, suspension agents, binders, lubricants and the like, may be present in the formulation.

The pharmaceutical preparations, suitable for oral use, may be in the form of tablets, capsules, granules in monodose sachets, or multidose granules.

The tablets may be film-coated.

The pharmaceutical formulations according to the present invention may be obtained by the methods known to the persons skilled in the art. For example, a method for the preparation of the formulation of the invention, comprises the preparation of granules by mixing, in a suitable mixer, all the raw materials previously sieved and weighted. The thus obtained granules can be:

a) directly compressed, for example with oblong pressing punches, in order to obtain tablets to be directly swallowed, or
b) compressed, for example with circular pressing punches having a large diameter, and then sieved, and the thus obtained granules can be used in the other forms of pharmaceutical preparations.

In the case of a), wherein the powder is used in order to produce tablets of 1 g of amoxicillin, it is necessary to optimize the compression conditions for obtaining tablets with a hardness of from 7 to 10 kg and an average weight of about 1.4 g (variable according the title of the active principle). Said tablets may be coated with a film of an aqueous suspension of ethylcellulose, titanium dioxide, polyethylene glycol 4000, polyethylene glycol 6000.

In the case of b), wherein the granulate is intended for the production of other forms of oral pharmaceutical preparations, said granules must be compressed, for example with circular pressing punches, by optimizing the compression conditions so as to obtain tablets having a hardness of from 8 to 12 kg. The thus obtained tablets are then sieved to obtain granules which will be used in the production of the other forms of pharmaceutical preparations.

The pharmaceutical formulations according to the present invention provide therapeutic levels of amoxicillin in the blood for 12 hours, therefore two

administrations of amoxicillin per day being sufficient. This fact considerably improves the compliance of patients especially in the case of children.

Furthermore the levels of amoxicillin in the blood are maintained constant in the course of the time without the sharp variations of concentration stemming from the repeated administrations of amoxicillin

Fig.1 shows a graph reporting the plasma concentration of amoxicillin (mg/l), at Example 1, to five adults.

EXAMPLE 1

1g AMOXICILLIN TABLETS (not coated)

Amoxicillin trihydrate	1148 mg
(corresponding to 1g of amoxicillin)	
Hydroxypropyl methylcellulose	90 mg
Soybean hydrogenated phosphatidylcholine	70 mg
Sodium carboxymethylcellulose	90 mg
Magnesium stearate	20 mg

2296 g trihydrate amoxicillin, 180 g hydroxypropyl methylcellulose (Methocel K 4M), 140 g soybean hydrogenated phosphatidylcholine (Epikuron 200 SH), 180 g sodium carboxymethylcellulose (Pharmacel XL), 40 g magnesium stearate, previously sieved through a sieve having a hole of 1 mm as net aperture, were placed in a conical mixer.

The thus obtained granules were compressed with oblong pressing punches to obtain tablets to be swallowed.

EXAMPLE 2

1g AMOXICILLIN TABLETS (coated)

Amoxicillin trihydrate	1148 mg
(corresponding to 1g of amoxicillin)	
Hydroxypropyl methylcellulose	90 mg
Soybean hydrogenated phosphatidylcholine	70 mg

Sodium carboxymethylcellulose	90 mg
Magnesium stearate	20 mg
COATING*	32 mg

* Ethylcellulose-titanium dioxide-polyethylene glycol 4000- polyethylene glycol 6000 in the weight ratio 14:14:2:2.

The tablets were obtained according to the method of Example 1 and then coated with a film having the above reported composition.

EXAMPLE 3

AMOXICILLIN GRANULES IN 1 g MONODOSE SACHETS (for adults)

Amoxicillin trihydrate	1148 mg
(corresponding to 1g of amoxicillin)	
Hydroxypropyl methylcellulose	90 mg
Soybean hydrogenated phosphatidylcholine	70 mg
Sodium carboxymethylcellulose	90 mg
Magnesium stearate	20 mg
Xanthan gum	6 mg
Raspberry flavour	71 mg
Strawberry flavour	25 mg
Sucrose	2498 mg

2296 g trihydrate amoxicillin, 180 g hydroxypropyl methylcellulose (Methocel K 4M), 140g soybean hydrogenated phosphatidylcholine (Epikuron 200 SH), 180 g sodium carboxymethyl cellulose (Pharmacel XL), 40 g magnesium stearate, previously sieved through a sieve having a hole of 1 mm as net aperture, were placed in a conical mixer.

The thus obtained granules were compressed with circular pressing punches, obtaining tablets which were then sieved throuth a sieved having a hole of 0.66 mm as net aperture.

The granules obtained were then mixed with the other excipients.

EXAMPLE 4

AMOXICILLIN GRANULES IN 250 mg MONODOSE SACHETS (for children)

Amoxicillin trihydrate (corresponding to 250 mg of amoxicillin)	287 mg
Hydroxypropyl methylcellulose	22.5 mg
Soybean hydrogenated phosphatidylcholine	17.5 mg
Sodium carboxymethylcellulose	22.5 mg
Magnesium stearate	5 mg
Xanthan gum	3 mg
Raspberry flavour	71 mg
Strawberry flavour	25 mg
Sucrose	3059 mg

The formulation was prepared according to the method reported for Example 3.

EXAMPLE 5

AMOXICILLIN GRANULES TO BE DOSED, 250 mg amoxicillin/3 g granules (bottle containing 50 g)

Amoxicillin trihydrate (corresponding to 250 mg of amoxicillin)	287 mg
Hydroxypropyl methylcellulose	22.5 mg
Soybean hydrogenated phosphatidylcholine	17.5 mg
Sodium carboxymethylcellulose	22.5 mg
Magnesium stearate	5 mg
Xanthan gum	3 mg
Raspberry flavour	71 mg
Strawberry flavour	25 mg
Sucrose	2562 mg

The formulation was prepared according to the method reported for Example 3.

EXAMPLE 6

Dissolution test

The dissolution test was performed according to USP XXIII.

The results of the test are reported in the following table, as release percentages at different times, for six tablets (A-F) obtained as reported in the Example 1.

Tablet	Weight (g)	% release 1 h	% release 1.5 h	% release 3 h	% release 4 h	% release 5 h	% release 6 ore	% release 7 h	% release 8h
A	1.392	20.1	26.2	42.8	51.9	61.3	68.4	74.4	**76.3**
B	1.387	19.7	25.7	40.3	50.6	58.7	65.0	70.4	**75.5**
C	1.390	20.8	26.5	41.8	48.5	61.3	66.5	73.0	**76.4**
D	1.390	19.9	26.7	42.8	51.3	62.3	67.7	73.6	**78.8**
E	1.382	17.9	24.8	47.2	55.6	66.3	70.6	79.4	**86.7**
F	1.409	24.0	30.2	45.6	54.3	65.4	73.3	72.2	**84.0**
Average	**1.392**	**20.4**	**26.7**	**43.4**	**52.0**	**62.6**	**68.6**	**74.7**	**79.6**
S.D.	**0.01**	**1.83**	**1.69**	**2.32**	**2.34**	**2.59**	**2.72**	**2.92**	**4.25**
C.V.%	**0.60**	**8.99**	**6.34**	**5.33**	**4.50**	**4.14**	**3.96**	**3.91**	**5.34**

CLAIMS

1) A pharmaceutical formulation of amoxicillin for oral administration, comprising a homogeneous mixture of amoxicillin and one or more polysaccharides.
2) A pharmaceutical formulation according to claim 1, wherein the polysaccharide is selected from the group consisting of regenerated cellulose, cellulose ethers or esters, xanthan gum or carrageenan.
3) A pharmaceutical formulation according to claim 2, wherein the cellulose ethers or esters are methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose.
4) A pharmaceutical formulation according to any one of the preceding claims further containing a clavulanic acid salt.
5) A pharmaceutical formulation according to claim 4 wherein the clavulanic acid salt is the potassium salt.
6) A pharmaceutical formulation according to any one of the preceding claims further containing a surfactant.
7) A pharmaceutical formulation according to claim 6, wherein the surfactant is a phospholipid natural or synthetic (hydrogenated phospholipide).
8) A pharmaceutical formulation according to claim 7 wherein the surfactant is a phospholipid selected from a group consisting of phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine and their hydrogenated forms.
9) A pharmaceutical formulation, according to claim 8, wherein the surfactant is hydrogenated phosphatidylcholine.
10) A pharmaceutical formulation according to any one of the preceding claims further containing one or more excipients.
11) A pharmaceutical formulation according to any one of the preceding claims for oral use.

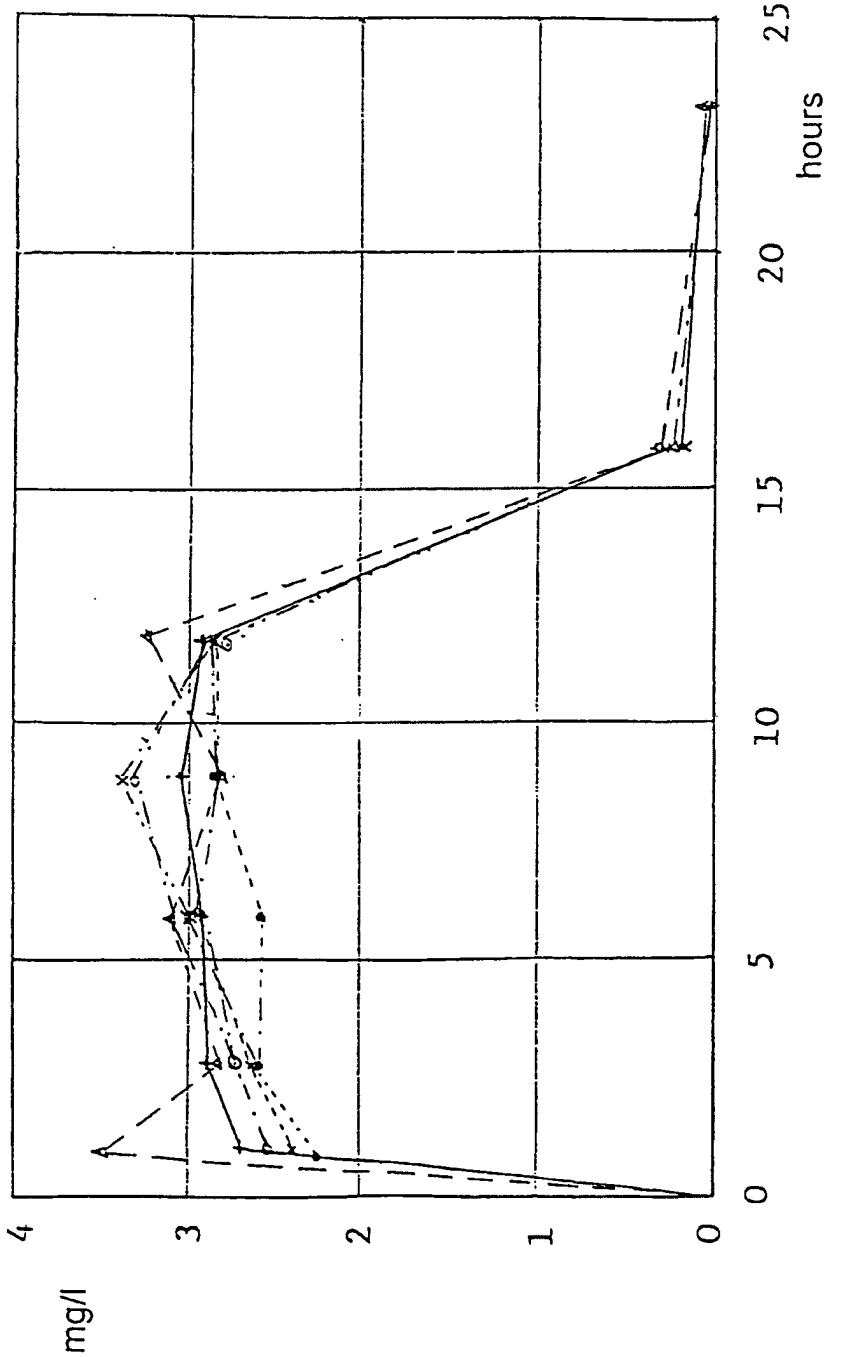

Fig. 1

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/16 A61K31/43

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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